UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/749,025	12/27/00	NUIJTEN	P 99511 US

HM12/0703

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EXAMINER	
FORD, V	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 07/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/749,025	Applicant(s) NUIJTEN ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Claim Rejections

1. Claims should be the subject of a complete sentence and should begin with "I claim", "We claim", "What is claimed is" or some equivalent.

Specification

2. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

3. The specification is objected to because of the following informalities: The specification is objected to because of what appear to be typographical errors. For example, page 6, line 15 recites the term "hybridisation which should be changed to "hybridization" and page 15 line 23 recites the term " mutagenised" which should be changed to "mutagenized". Applicant is asked to review the entire specification for typographical errors. Appropriate correction is required.

Drawings

4. The drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 498.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

5. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 is drawn to a mutated *Salmonella* strain according claim 1 having the same immunological characteristics as the strain that has been deposited with the Centrallbeureau voor Schimmelcultures under accession number 108955.

Because it is not clear that cell lines possessing the properties of *Salmonella* strain 108955 are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of a suitable deposit for patent purposes a deposit in a public repository is required. Without a publicly available deposit of the above *Salmonella* strain 108955, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's does not refer to a deposit of *Salmonella* strain 108955 in the specification, therefore there is no assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full

street address of the depository is required. If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

> (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;
>
> (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;
>
> (c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
>
> (d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the repository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the *Salmonella* strain 108955 described in the claims as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

6. Claims 2-3, 5 and 7 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Claims 2-3, 5 and 7 are drawn to a mutated bacterium of the genus *Salmonella* that lacks at least one antigenic determinant of flagellan or flagella due to a mutation in the flagellin gene.

Despite the knowledge in the art for the isolation of *Salmonella* strains, the specification fails to provide guidance regarding how the *Salmonella* strain is mutated. A mutated *Salmonella* strain is recited in the claims. The specification does not provide enablement for the *Salmonella* strain used in the claimed invention. The specification discloses that much is currently known about the synthesis of flagellin and the

subsequent maturation into flagella. The process of flagella biogenesis requires the concerted action of a large number of genes, not only the gene encoding the flagellin but also a large number of genes involved in the synthesis of the flagellum and the flagellar motor. The specification also discloses that there are two approaches for making bacteria according to the claimed invention. First, all mutations can be made in genes encoding the flagellin protein in order to mutate one or more antigenic determinants. Secondly, one or more genes involved in the biogenesis pathway of the flagellum can be mutated (p. 5). Which of the above approaches was used to make the mutated *Salmonella* strain used in the claimed invention? If the first approach was used, what nucleotide bases where deleted in the gene that encodes the flagellin protein? Were there insertions or substitutions used in the nucleotide sequence that encodes the flagellin protein to make the mutated *Salmonella* strain? If the second approach was used, which genes in the biogenesis pathway of the flagellum were mutated? How were they mutated ? Were deletions, insertions or substitutes used in the nucleotide sequences of the genes in the biogenesis pathway to make the mutated *Salmonella* strain?

Despite what is disclosed in the specification regarding the synthesis of flagellin and the maturation of flagella, the specification fails to teach how to make or use the mutated *Salmonella* strain of the claimed invention. Therefore, one of skill in the art would require guidance, in order to make or use the claimed invention in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 4 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims should spell out the genus and species at the first appearance in the claims.

8. Claim 6 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites "immunological characteristics", because it is unclear as to what the applicant is referring?

9. Claim 7 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites "immunological effective amount" because it is unclear as to what the applicant is referring?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as anticipated by Anderson *(GB Patent No. 1,109,179, published April 10, 1968, The London Patent Office)*.

Claim 1 and 4-6 are drawn to a mutated bacterium of the genus *Salmonella* that in its wild form carries flagella, said bacterium lacks at least one antigenic determinant of flagellin or flagella found in its wild type form.

Anderson teaches stable non-motile strains of *Salmonella typhi* and *Salmonella paratyphi* (A and B) which are devoid of flagella capable of producing theTH, AH or BH antibodies (p. 1, lines 51-55). The TH antigen is constituted by the flagella, which is responsible for its mobility, and the antibodies produced by this antigen are correspondingly known as TH antibodies (p. 1, lines 21-32).

Since the Office does not have the facilities for examining and comparing applicant's *Salmonella* strain with the *Salmonella* strain of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the *Salmonella* strain of the prior art does not possess the same material structural and functional characteristics of the claimed *Salmonella* strain). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

11. Claims 1-6 are rejected under 35 U.S.C. 102(b) as anticipated by He et al *(Journal of Bacteriology, April 1994, p. 2406-2414).*

Claims 1-6 are drawn to a mutated bacterium of the genus *Salmonella* that in its wild form carries flagella, said bacterium lacks at least one antigenic determinant of flagellin or flagella due to a mutation in the flagellin gene.

He et al teach *Salmonella* mutants that have deletions and amino acid alterations in the hypervariable region IV and the regions of putative epitopes. The expressed product of most of the mutant genes, with deletions up to 92 amino acids in region IV, assembled into functional flagella and conferred motility on the flagellin-deficient hosts. Functional analysis of the mutants suggested that the hypervariable region is important in the function of the flagella. The hybrid proteins formed by insertion of peptide sequence of hepatitis B virus surface antigen into the deleted flagellins assembled into functional flagella and antibody to the peptide sequence was detected after immunization of mice with the hybrid protein. This suggests that such mutant flagellins containing heterologous epitopes have potential as vaccines (see Abstract).

Since the Office does not have the facilities for examining and comparing applicant's *Salmonella* strain with the *Salmonella* strain of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the *Salmonella* strain of the prior art does not possess the same material structural and functional characteristics of the claimed *Salmonella* strain). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

12. Claims 7-11 are rejected under 35 U.S.C. 102(b) as anticipated by Anderson *(GB Patent No. 1,109,179, published April 10, 1968, The London Patent Office).*

Claims 7-11 are drawn to a vaccine for protection against Salmonellosis comprising an immunogenically effective amount of bacteria as defined in claim 1 or antigenic material thereof and a pharmaceutically acceptable carrier.

Anderson teaches a killed anti-typhoid vaccine or anti-typhoid vaccine formulation for parenteral administration to humans in which the protective antigen is a stable non-motile strain of *Salmonella typhi* or *Salmonella paratyphi* A or B which is devoid of flagella capable of producing the corresponding TH, AH, or BH antibodies. The vaccines can be produced in freeze-dried or liquid form. Heat-killed phenolized, acetone-killed, alcohol-killed and dried vaccines may be prepared. For use in man, vaccines prepared according to this invention are administered in the same way as traditional vaccines, i.e. by subcutaneous or intradermal routes (p. 2, lines 45-59).

Limitations such as the use of adjuvants would be inherent in the vaccine of the prior art. Limitations such as "a vaccine for the protection of animals against Salmonellosis" is being viewed as an intended use limitation which carries very little patentable weight to the product.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the vaccine of the prior art does not possess the same material

structural and functional characteristics of the claimed *Salmonella* vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

13. Claims 7-11 are rejected under 35 U.S.C. 102(b) as anticipated by He et al *(Journal of Bacteriology, April 1994, p. 2406-2414).*

Claims 7-11 are drawn to a vaccine for protection against Salmonellosis comprising an immunogenically effective amount of bacteria as defined in claim 1 or antigenic material thereof and a pharmaceutically acceptable carrier.

He et al teach *Salmonella* mutants that have deletions and amino acid alterations in the hypervariable region IV and the regions of putative epitopes. The expressed product of most of the mutant genes, with deletions up to 92 amino acids in region IV, assembled into functional flagella and conferred motility on the flagellin-deficient hosts. Functional analysis of the mutants suggested that the hypervariable region is important in the function of the flagella. The hybrid proteins formed by insertion of peptide sequence pre-S1 12-47 of hepatitis B virus surface antigen into the deleted flagellins assembled into functional flagella and antibody to the pre-S1 sequence was detected after immunization of mice with the hybrid protein. This suggests that such mutant flagellins containing heterologous epitopes have potential as vaccines (see Abstract).

He et al further teach that the *Salmonella* mutants mixed with MPL+ TDM emulsion containing 50 μg of each adjuvant, MPL and S-TDCM, per 0.2 ml (mouse dose) were injected into mice by intraperitoneal injection.

The composition of He et al is the same as the claimed vaccine. The criticality of limitations such as "freeze-dried" or "spray-dried" has not been established, are being viewed as process limitations [illegible] and would be a matter of design choice.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed *Salmonella* vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Pertinent Prior Art

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Cox et al, Vaccine, Volume 15 Number 3, 1997, p. 248-256).*

Status of Claims

15. No claims are allowed.

Conclusion

16. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
June 29, 2001

L. F. Smith

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